REMARKS

Claim 1 has been amended to add the phrase "resulting from a dopamine-related dysfunction" in reference to Parkinson's disease. This amendment was made to clarify the nature of the disorder that is treatable by the claimed method. Support for this amendment is found throughout the specification.

Claims 1-12 stand rejected under 35 U.S.C. 112, first paragraph, for lack of enablement. The Examiner contends that Applicants' specification only enables a method for treating Parkinson's disease comprising administering dinapsoline according to the steps set forth in claim 1, and not a method comprising administering a "D_1 agonist," as claimed. The Examiner contends that the specification does not enable the person of ordinary skill in the art to practice the invention commensurate in scope with claims 1-12. The Examiner cites the Wands factors: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) predictability of the prior art; (E) the guidance of the specification; (F) the existence of working examples; and (G) the amount of experimentation necessary.

Applicants do not believe that the Examiner has met her burden of showing why the invention recited in claims 1-12 is not enabled. *See generally In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Further, Applicants respectfully disagree with the Examiner's reading of the instant specification. The captioned application enables the skilled artisan to practice the invention of claims 1-12. In support of this contention, Applicants submit herewith a declaration from Dr. Richard B. Mailman under 37 C.F.R. § 1.132 demonstrating that Applicants' specification is enabling for the breadth of claims 1-12 as amended.

The purpose of the enablement requirement is to ensure that the invention is communicated to the public in a meaningful way. The test of enablement is simply whether the specification as a whole is sufficient to enable the person of ordinary skill in the art to make and use the invention. This question has been articulated as a set of factors known as the *Wands* factors. However, it is important to note that an applicant has not failed to satisfy the enablement requirement though experimentation by the person of ordinary skill in the art is needed. The standard for lack of enablement is the need for *undue experimentation* by the ordinarily skilled artisan. *See* MPEP § 2164.01.

In the Office Action dated July 15, 2003, the Examiner states that "the nature of the invention is extremely complex in that it encompasses the actual treatment of Parkinson's disease comprising the reducing D_1 agonist dose in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance." The

Examiner further states that the complex nature of the claims is "greatly exacerbated by breadth of claims," and that Parkinson's disease "has potentially many different causes."

The Examiner indicates that "the state of the art is relatively high with regard to treatment of Parkinson's disease with a D_1 agonist with continual administration with optimal activation of D_1 receptors." Moreover, the Examiner concedes that there are not "any examples or teaching in the prior art wherein a compound similar to the claimed compounds was administered to a subject to result in suboptimal activation of D_1 receptors." Applicants agree that it is heretofore unknown that a Parkinson's disease treatment may include reducing the full dopamine D_1 agonist dose to achieve a suboptimal activation of D_1 dopamine receptors so that tolerance is not induced, as claimed by Applicants. Indeed, that which the Examiner does not find in the prior art is Applicant's invention.

Applicants' invention is not complex. Applicants' claims simply require the administration of a full D_1 agonist with a half-life of less than 6 hours and reducing the dose of the D_1 agonist at least once every 24 hours to lower the concentration of agonist so that tolerance is not induced. There is nothing complex about these steps and the person of ordinary skill in the art can read the specification and readily recognize how to carry out these steps to obtain a second lower tissue concentration of agonist once every 24 hours wherein said second concentration of agonist results in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance, as supported by the declaration of Dr. Richard B. Mailman submitted herewith.

Applicants respectfully suggest that the Examiner is confusing the complexity of Parkinson's disease with Applicants' claimed method for treating this disease. The Examiner states that Parkinson's disease "has potentially many different causes (i.e. many different neuronal degradation or combination of degradations)." Indeed, Parkinson's disease is complex. Nevertheless, Applicants' method for treating a patient with Parkinson's disease resulting from dopamine-related dysfunction is not "extremely complex."

Further, the breadth of the claims does not exacerbate the nature of Applicants' claims. Applicants have amended the claims to clarify that the claimed method is for treating a patient suffering from Parkinson's disease "resulting from a dopamine-related dysfunction." As currently claimed, Parkinson's disease resulting from a dopamine-related dysfunction is treated with a full D_1 agonist by following the claimed dosing regimen. Moreover, Applicants indicate that dopamine has been implicated in the etiology and treatment of several neurological and psychiatric disorders, including Parkinson's disease, and state that "Parkinson's disease results from insufficient dopaminergic activity." P. 1, ll.

16-24. Thus, the treatment of Parkinson's disease "resulting from a dopamine-related dysfunction" as claimed is addressed by the administration of a full D_1 agonist.

Furthermore, Applicants' claims require that the administered compounds are full D_1 agonists, and in addition, that these full D_1 agonists have half-lives of less than six hours. These compounds form a narrowly defined group. In fact, compounds that exhibit agonistic functionality are generally uncommon. In addition to recognition by and binding to a receptor, an agonist unlike an antagonist must elicit the same functional behavior as the native ligand upon binding. Therefore, D_1 dopamine receptor agonists have to behave functionally as would dopamine. Moreover, Applicants' claims require that the administered compounds are full agonists. Partial agonists that behave functionally like dopamine, but cannot elicit a full functional effect, are not included in the group specified in the claims. The full D_1 agonists are even more narrowly specified in the claims because the full D_1 agonists must have half-lives of less than 6 hours. This narrowly defined group of highly specific and specialized D_1 agonists does not represent a group having undue breadth, and a claim that specifies such a group of D_1 agonists cannot be fairly characterized as overbroad.

The Examiner also indicates that the guidance provided by the specification is minimal and is directed to dinapsoline rather than any D_1 agonist, all of the working examples are directed to dinapsoline, and that the lack of guidance makes practicing the invention with any D_1 agonist unpredictable. Therefore, the Examiner concludes that the amount of experimentation necessary to practice the invention is undue.

The Examiner acknowledges that Applicants' description is enabling for dinapsoline because Applicants have described in great detail how to use dinapsoline in the claimed method. The MPEP indicates that Applicants are not required to describe all actual embodiments. *See generally* § 2164.02. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP § 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)).

Furthermore, the Examiner has not explained why dinapsoline is incapable of being a representative member of the specified genus of full D_1 agonists, as required by MPEP § 2164.02. "In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not

adequately enabled by the disclosure)." MPEP § 2164.04. The Examiner only states that "[a]ll of the working examples provided by the specification are directed toward the treatment of Parkinson's disease with dinapsoline," and that "[a]ll of the guidance provided by the specification is directed towards treatment with dinapsoline rather than any D_1 dopamine agonist." These statements are merely conclusions and do not explain why the working examples for dinapsoline coupled with the detailed description provided in Applicants' specification are insufficient to enable the claimed method using any full D_1 agonist.

Applicants believe that the working example provided by the exemplification of the full D_1 agonist dinapsoline is generally illustrative of the invention, which includes administering a full D_1 agonist in a method for treating Parkinson's disease. Applicants also teach other full D_1 agonists, including dinoxyline and dihydrexidine. *See* pp. 27-32; Example 2. In addition, Applicants teach that dinapsoline, dinoxyline, and dihydrexidine have all been shown to be efficacious in Parkinson's disease models, such as the unilateral 6-OHDA-lesion rodent model. *See* p. 9, ll. 2-4; Example 3, pp. 33-35. Applicants also state that "the pharmacological properties of these two molecules are similar," as supported by observing the space filling representations of the low energy conformations of dihydrexidine and dinoxyline. P. 14, l. 28; *see also* pp. 15-16 (discussing the pharmacological properties of dinapsoline and dinoxyline). The person of ordinary skill in the art will appreciate that the claimed method is not limited to a method using dinapsoline.

Contrary to the Examiner's assertion, Applicants have provided sufficient guidance in the specification to enable the invention of claims 1-12. Exemplary pharmaceutical formulations and routes of administration are described in the specification. *See generally* pp. 17-20. Full D_1 agonists are described, and the specification details how the skilled artisan may identify other full D_1 agonists fitting the criteria required by the claims by providing specific procedures for determining half-lives, functional behavior, and full or partial agonist behavior. P. 16, ll. 6-12. Applicants have also described what is meant by a half-life of less than 6 hours. *See* Example 4; Fig. 1. Furthermore, Applicants have described exemplary doses for producing a therapeutic effect (p. 16, l. 19 to p. 17, l. 11), and how to reduce the dose of D_1 the agonist at least once every 24 hours (p. 4, ll. 9-10). Applicants have also described an appropriate animal model system, the unilateral 6-OHDA-lesion model for Parkinson's disease, for evaluating full D_1 agonists. *See* pp. 33-35; Example 3.

In addition, Applicants define suboptimal activation as a state where "receptors either are not activated, or are not fully activated." P. 6, ll. 26-27. Simply stated,

suboptimal activation results when the treatment with the D_1 agonist is discontinued or a lower dose is administered so that the optimal therapeutic effect is no longer observed. Methods for measuring suboptimal activation are described in the specification (p. 7, ll. 8-25) and in the declaration of Dr. Richard B. Mailman submitted herewith.

The data discussed in the declaration of Dr. Richard B. Mailman submitted herewith under 37 C.F.R. § 1.132 show that other dinapsoline and other full D_1 agonists, such as dihydrexidine and A77636, cause tolerance when administered continuously over a 24-hour period. *See* Figure A. The data also show that when dihydrexidine is administered at a second lower dose within 24 hours, tolerance is not induced. *See* Figure B. Accordingly, Dr. Mailman states in paragraph 10 of the declaration: "The data in Figures A and B demonstrate that the captioned application does enable the use of full D_1 agonists, even those from different chemical classes, administered using the claimed method, to treat a patient with Parkinson 's disease resulting from a dopamine-related dysfunction." Paragraph 10. Furthermore, Dr. Mailman states in the same paragraph of the declaration: "[O]nly routine experimentation was required to determine the reduced dose of dihydrexidine required to obtain a second lower tissue concentration of agonist, upon minipump removal, that resulted in suboptimal activation of D_1 dopamine receptors for a period of time sufficient to prevent induction of tolerance." Paragraph 10.

The data discussed in the declaration of Dr. Richard B. Mailman also demonstrate that finding a suboptimal dose for dinapsoline is a simple process. *See* Figure C. When dinapsoline is administered continuously, tolerance is observed within 24 hours. *See* Figure C (top panel). However, simply administering one dose per 24 hour period (*see* Fig. 4 of the instant application) or two sequential doses spaced 12 hours apart results (*see* Figure C (bottom panel)) results in the suboptimal activation of the D_1 dopamine receptors for a period of time sufficient to prevent the induction of tolerance, as required by Applicants' claim 1. In contrast, administering three sequential doses at 9 hour intervals does not result in sufficient suboptimal activation of D_1 dopamine receptors, as required by claim 1, and tolerance is induced. *See* Figure C (middle panel). Dr. Mailman states in the declaration:

> The required reduced dose of the D_1 agonist, the suboptimal activation of D_1 dopamine receptors, and the period of time sufficient to prevent induction of tolerance were obtained by dosing the animals (6-OHDA-lesioned rats), as described in the specification of the captioned application, one or more times per day until tolerance was observed. In the case of dinapsoline, only three experiments were required to determine those doses (i.e. resulting from a dosing protocol) that were required to prevent the induction of tolerance.

Paragraph 14. Applicants respectfully contend that three experiments constitutes routine experimentation, and cannot be fairly characterized as undue experimentation.

The Examiner's analysis implies that any description requiring the person of ordinary skill in the art to optimize via experimentation necessarily involves an unacceptable quantity of experimentation needed to make or use the invention. However, as stated above, required experimentation is unacceptable only when the required experimentation is *undue*. The data discussed in the 1.132 declaration of Dr. Mailman shows that optimization of parameters based on Applicants' disclosure does not require an unacceptable quantity of experimentation. Furthermore, the data discussed in the declaration demonstrate that by using the experimental design described in the captioned application (i.e. the guidance of the specification), Dr Mailman showed that other full D_1 agonists from other chemical classes can be used in the claimed method. Thus, the guidance provided by the specification (i.e. in the specification and the working examples) is sufficient to enable the skilled artisan to practice Applicants' claimed method and the experimentation required to identify full D_1 agonists that can be used in the claimed method is not undue. Furthermore, the Examiner's assertion that "[t]he lack of significant guidance from the specification" makes practicing the claimed invention unpredictable cannot be correct because the data presented in the declaration of Dr. Mailman shows that the guidance provided by the specification does enable the skilled artisan to practice Applicants' claimed method.

Thus, Applicants believe they are entitled to a claim that covers any full D_1 dopamine agonist, and should not be limited to the exemplified embodiments. The MPEP states:

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

MPEP § 2164.02. Although Applicants respectfully contend that the Examiner has not met her burden of showing that Applicants' claims 1-12 lack enablement under 35 U.S.C. § 112, Applicants nevertheless proved that the present application is enabling for the invention of claims 1-12. *See generally* Dr. Mailman's declaration. Applicants provided representative examples (i.e. dinapsoline) in the application, together with a description of additional full D_1 agonists for use in the Applicants' claimed method, with the expectation that any full D_1

agonist could be used in the claimed method. Moreover, Applicants proved without undue experimentation that other full D_1 agonists can be used in Applicants' claimed method. Thus, Applicants' are entitled under MPEP § 2164.02 to claims 1-12 as amended.

For the foregoing reasons, Applicants believe that the invention defined by claims 1-12 is enabled by the instant application, and claims 1-12 are in condition for allowance. Applicants respectfully request that the Examiner reconsider her rejection under 35 U.S.C. § 112, and pass the application to issuance.

Respectfully submitted,
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